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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/079,758	05/15/98	MORRISON D	MSC-22939-1-

HM12/0730

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1616	5

DATE MAILED: 07/30/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/079,758	Applicant(s) Morrison et al
	Examiner Shahnam Sharareh	Group Art Unit 1616

☒ Responsive to communication(s) filed on *5/15/98, 6/28/99* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-59 and 69-71* is/are pending in the application.

Of the above, claim(s) 60-68 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-59 and 69-71* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election

1. Applicant's election with traverse of Group I in Paper No. 4 is acknowledged. The traversal is on the ground(s) that although the restricted groups have a different modes of operation, but the subject matter of all of the claims is related and that a search of art related to any of the groups will be applicable or relevant to the claims of the others. This is not found persuasive because in the instant case treating tumor may be done by other non-microcapsulated therapies, or the claimed microcapsule may have a different utility in other area of medical science such as diagnostic testings. Further the claimed microcapsule can also be prepared by other means of manufacturing known in the art, subsequently a different search is required for each group of inventions. Therefore, a restriction for examination purposes as indicated in Paper No. 4 is proper. However, Examiner has reconsidered the request of the applicant and will rejoin Group II (the claims directed to method of controlling the release of a drug), previously withdrawn from consideration as a result of a restriction requirement. Thus, claims 1-59, and 69-71 are pending in this application, and claims 60-68 are withdrawn from consideration as being directed to a non-elected invention.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

3. In the instant case, the U.S. application Serial No. 08/349,169 filed December 2, 1994, now U.S. Patent No. 5,827,531 fails to teach a microcapsule comprising energy absorbing components such as graphite, aluminum powder or TWEEN, or drugs such as anesthetics, antiparasitics, or antibiotics such as erythromycin, or gentamicin. In addition, above mentioned application also fails to teach the claimed method of controlled drug delivery to a patient, and further the claimed method of treating a tumor.

Although some of the broad claims may have support to earlier filed priority applications, the effective priority date used for the examination of the instant application is May 15, 1998.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 3 and 4 recite the limitation "energy absorbing medium" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

6. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim's recitation of "at least internal hydrocarbon phase" renders the claim vague and confusing.

7. Claim 69 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim recites ".. a first portion of said micro capsules has a polymer outer membrane with a different melting point than a second portion of said micro capsules, and further wherein both the first and second melting points are lower than the Curie point of the magnetic particles." The recitation of " first portion of said microcapsule" and further "second portion of said microcapsule" is confusing because it is not clear what portions does the applicant refer to.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 7, 21, 40, 44, 51-52, 56-59 rejected under 35 U.S.C. 102(b) as being anticipated by Mathiowitz et al US Patent 4,898,734.

The instant claims are directed to a microcapsule comprising one or more internal, immiscible liquid phases enclosed within a polymer outer membrane; at least one energy absorbing component in an internal liquid phase in contact with the outer membrane; and a drug or drug precursor contained in a pharmaceutically acceptable solution. The instant claims are also drawn

to methods of delivering said microcapsule comprising administering the drug delivery solution to a subject and exposing the microcapsule to an energy source.

Mathiowitz et al US Patent 4,898,734 disclose methods for making and delivering a composition comprising a polymer outer membrane, one internal containing immiscible liquid phase, an energy absorbing component, and a drug; wherein said composition is contained in a pharmaceutically acceptable carrier monitoring step, and a step comprising releasing of a therapeutic agent in desired regions of the patients using an energy source (see abstract, col 4 lines 9-35 & 40-66, col 5 lines 21-40 & 50-65, col 6 lines 5-14 & 58-68, col 7 lines 1-15, col 8 1-25). Therefore Mathiowitz et al meets the limitation set forth in the instant claims.

10. Claims 1-3, 6-10, 13-16, 30-35, 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Radhakrishnan US Patent 5,049,389.

The instant claims are drawn to microcapsules comprising one or more internal containing immiscible liquid phases; an outer polymer membrane comprising groups such as cholesterol, polyvinyl alcohols or lecithins; one or more energy absorbing components in an internal liquid phase, such as graphite or TWEEN, in contact with the outer membrane; a drug or drug precursor wherein said drug or drug precursor is an antibiotic, an anti-cancer drug, an antifungal, or an antiinflammatory; and further said microcapsules are in a pharmaceutically acceptable solution.

Radhakrishnan in US Patent 5,049,389 disclose a lipid particle formulation for controlled drug delivery of steroids comprising one or more internals (see col 9 lines 35-68 and col 10 lines 1-25), lipid components such as cholesterol or lecithins; TWEEN containing micelle (see col 14

lines 45-68, col 15 lines 1-20); various drug or drug precursors selected from therapeutic classes such as antibiotics, anti cancer, antiinflammatory, antifungal, in a pharmaceutically acceptable solution. Therefore, Radhakrishnan meets the limitations set forth in the instant claims.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

11. Claims 1-59, 69-71 rejected under 35 U.S.C. 102(e) as being anticipated by Unger et al. US Patent 5,853,752.

The instant claims are drawn to microcapsules comprising one or more internal containing immiscible liquid phases; an outer polymer membrane comprising groups such as glycerol monosterate, cholesterol, polyvinyl alcohols or lecithins; one or more energy absorbing components in an internal liquid phase, such as graphite, TWEEN, or an oil in contact with the outer membrane; a magnetic particle; a drug or drug precursor wherein said drug or drug precursor is an antibiotic, an anti-cancer drug, an antifungal, an anesthetic, an antiviral, a thrombolytic agent, or an antiinflammatory; and further said microcapsules are in a pharmaceutically acceptable solution. The instant claims are also drawn to methods of delivering said microcapsule comprising administering the drug delivery solution to a subject and exposing the microcapsule to an energy source.

Unger et al in US Patent 5,853,752 disclose a liposome for controlled drug delivery of pharmaceutically active agents utilizing an energy source (see col 25 lines 17-22, col 40 lines 20-29) comprising one or more internals; an outer polymer membrane comprising groups such as

lipids, cholesterol or lecithins (see col 20 line 46-67, col 21 & 22); an emulsifying agent such as TWEEN or sorbitan monooleate ; an suspending agent such as glycerol, alginate, aluminum monosterate, aluminum silicate (see col 23 lines 39-66 and col 25 lines 59-67); a paramagnetic particle (see col 33 lines 46-55); various drug or drug precursors selected from therapeutic classes such as antibiotics, anti cancer, antiinflammatory, antifungal (col 32 lines 37-60, col 33 lines 46-67, col 34-35), in variety of sizes (see col 27 lines 11-41) delivered to specific sites via a pharmaceutically acceptable solution (see col 26 lines 3-30). Unger et al also disclose methods of delivering said microcapsule comprising administering the drug delivery solution to a subject and exposing the microcapsule to an energy source (col 40 lines 20-30). Therefore, Unger et al meet the limitations set forth in the instant claims.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-43, and 69-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathiowitz et al US Patent 4,898,734, Grinstaff et al US Patent 5,508,021 and Radhakrishnan US Patent 5,049,389 and Unger et al US Patent 5,853,752.

The instant claims are drawn to micro capsules comprising one or more internal containing immiscible liquid phases; an outer polymer membrane comprising groups such as glycerol

monosterate, cholesterol, polyvinyl alcohols or lecithins; one or more energy absorbing components in an internal liquid phase, such as graphite, TWEEN, or an oil in contact with the outer membrane; a magnetic particle; a drug or drug precursor wherein said drug or drug precursor is an antibiotic, an anti-cancer drug, an antifungal, an anesthetic, an antiviral, a thrombolytic agent, or an antiinflammatory; and further said microcapsules are in a pharmaceutically acceptable solution.

Mathiowitz et al US Patent 4,898,734 disclose methods for making a composition comprising a polymer outer membrane, one internal containing immiscible liquid phase, an energy absorbing component, and a drug; wherein said composition is contained in a pharmaceutically acceptable carrier monitoring step, and a step comprising releasing of a therapeutic agent in desired regions of the patients using an energy source

Grinstaff et al in US Patent 5,508,021 teaches a polymeric shell comprising an outer polymer membrane, an energy absorbing component such as metal particles selected from the group consisting of iron, iron oxide, and manganese; a biocompatible dispersing agent such as soybean oil, corn oil, cotton seed oil, in a pharmaceutically acceptable carrier (see col 5, col 8 lines 25-55, col 12 lines 1-44, col 17 lines 16-67, col 18 lines 1-20, col 36 lines 15-67, col 37-38.)

Radhakrishnan in US Patent 5,049,389 disclose a lipid particle formulation for controlled drug delivery of steroids comprising one or more internals (see col 9 lines 35-68 and col 10 lines 1-25), lipid components such as cholesterol or lecithins; TWEEN containing micelle (see col 14 lines 45-68, col 15 lines 1-20); various drug or drug precursors selected from therapeutic classes

such as antibiotics, anti cancer, antiinflammatory, antifungal, in a pharmaceutically acceptable solution.

Unger et al in US Patent 5,853,752 disclose a liposome for controlled drug delivery of pharmaceutically active agents utilizing an energy source (see col 25 lines 17-22, col 40 lines 20-29) comprising one or more internals; an outer polymer membrane comprising groups such as lipids, cholesterol or lecithins (see col 20 line 46-67, col 21 & 22); an emulsifying agent such as TWEEN or sorbitan monooleate ; an suspending agent such as glycerol, alginate, aluminum monosterate, aluminum silicate (see col 23 lines 39-66 and col 25 lines 59-67); a paramagnetic particle (see col 33 lines 46-55); various drug or drug precursors selected from therapeutic classes such as antibiotics, anti cancer, antiinflammatory, antifungal (col 32 lines 37-60, col 33 lines 46-67, col 34-35), in variety of sizes (see col 27 lines 11-41) delivered to specific sites via a pharmaceutically acceptable solution (see col 26 lines 3-30).

Microspheres and liposomes are readily used in pharmaceutical industry as a drug delivery vehicle. Mathiowitz, Radhakrishnan, Grinstaff and Unger teach the methods of making and the methods of utilizing microspheres or liposomes in drug delivery systems. Thus, the teachings of Mathiowitz, Radhakrishnan, Grinstaff and Unger are viewed as being in the same field of endeavor.

Although Grinstaff et al do not specifically teach the use of an energy source as means for drug delivery system, it would have been obvious to one of ordinary skill in the art to develop a microcapsule and further use an energy source utilizing the teachings of Mathiowitz and

Radhakrishnan and enhance the methods of delivering a therapeutic agent by creating an improved microcapsule that will release a therapeutic agent when exposed to an energy source.

Mathiowitz et al teach methods of making biodegradable microspheres and methods of delivering said microspheres to a site. Mathiowitz however fails to teach variety of therapeutic agents that can be encapsulated in a polymeric shell, thus it would have been obvious to one of ordinary skill in the art to improve methods of delivering a bioactive agent to a specific site by encapsulating various therapeutic compounds thought by Unger or Radhakrishnan and further utilize an energy source to enhance localized delivery of a drugs to a site of interest.

Furthermore, although Grinstaff et al do not specifically teach the use of an energy source as means for drug delivery system, it would have been obvious to one of ordinary skill in the art to develop a microcapsule and further use an energy source utilizing the teachings of Unger to improve micro capsules used for delivery of pharmaceutical agents and further methods of delivering a pharmaceutical agent to a specific site.

Conclusion

No claims were allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Sharareh whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Jose Dees can be reached on 703-308-4628. The fax phone number for this Group is 703-308-4556. Any inquiry

of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

Shahnam Sharareh, PharmD
sjs, July 21, 1999

JOSE' G. DEES
SUPERVISORY PATENT EXAMINER

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